Are We Giving Optimal Dose of Efavirenz?

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Antiretroviral is one of the drugs that extensively been studied for its drug-to- drug interaction. Its long term used and the fact that many HIV-infected patients came in the late stage of disease make polypharmacy is unavoidable.[1] Efavirenz is one of antiretroviral drugs that widely used in HIV-infected patients age more than 3 years old in many countries. Latest Indonesian antiretroviral guidelines recommend a combination of tenofovir, lamivudine and efavirenz given orally in one daily dose as the preferred primary fixed-drug combination treatment. This recommendation is based on many evidence supporting efficacy, tolerability, price, pregnancy safety, simplicity and the availability of the drug that will support the continuing comprehensive care for HIV-infected patients in primary care level.[2]

Since first being marketed in 1998, efavirenz has been dosed at 600 mg once a day for HIV-infected adults, either as efavirenz tablet of fixed-drug combination.[3] This drug often causes CNS-related symptoms that sometimes persist for a long period. This side effect frequently leads to treatment discontinuation or non-adhere to the treatment.

Efavirenz is extensively metabolized by the CYP2B2 isoenzyme group, particularly to the 8OH-EFV metabolite. It is also an autoinducer of its own metabolism via induction of CYP2B6.[4] Earlier study in caucasian population shown that concomitant use of rifampicin could decrease efavirenz plasma concentration up to 26%.[5] Therefore, it was recommended to raise the dose to 800 mg a day in patients with pre treatment bodyweight more than 50 kg. Different finding was reported in South Africa. Study by Orell, et al.[6] revealed that 600 mg efavirenz still retained adequate potency when giving concomitantly with rifampicin in HIV-infected patients with active tuberculosis.[6] However, combining rifampicin with other available NNRTI nevirapine could decrease nevirapine plasma concentration even more.[7] Therefore, efavirenz is still the preferred drug to be combined with rifampicin in many guidelines.[2]

Recently, questions have been raised about whether the dose of efavirenz could be reduced to 400 mg to lessen CNS-related effect and reduce cost without interfering the effectiveness. The ENCORE1 study first published in 2014 randomly assigned 639 antiretroviral naive patients who were starting treatment to either 400 mg or 600 mg efavirenz. About one third of participants in this study were Asian. Adverse events were significantly less frequent in the 400 mg group, recovery of CD4 lymphocytes was better in the 400 mg group, and proportions of patients with viral load suppression at 48 weeks were similar in both groups. HIV-infected patients with active tuberculosis were excluded in this study, hence it is unable to clarify the issue concomitant use of rifampicin with low dose efavirenz.[8] However, the newest WHO has started to recommend the use of 400 mg efavirenz as alternative first-line regiment in combination with tenofovir and lamivudine/or emtricitabine.[9]

This recommendation needs to be implemented carefully for Indonesian population. Study reported here by Mariana, et al[10] comparing HIV-infected Indonesian patients starting efavirenz-based antiretroviral therapy with and without the use of rifampicin revealed that there was large proportion of patients with sub-therapeutic efavirenz concentrations even in patients not receiving rifampicin. One of the plausible reasons is the possibility of many extensive metabolizer genotype in this population. Even though, in Indonesia, no studies have identified the CYP2B6 enzyme activity.

The impact of different therapeutic level of efavirenz to virological success can not be concluded in this study. Not only because of the small sample size, but also because of various time of viral load testing in defining the virologic suppression used in this study.[10]

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